

medicine was a relatively new field and the UW clinic was one of only five clinical training programs.

Dr Hammar also served as assistant and acting director of the UW Child Development and Mental Health Retardation Center, a University Affiliated Facility, from 1964-1965 and 1970-1971. In 1967 he took a sabbatical leave to study techniques of growth assessment in children and adolescents under James Tanner at the Institute of Child Health in London.

In 1971, Dr Hammar joined the JABSOM faculty and was appointed the Director of Ambulatory Services and Chief of Adolescent Medicine at Kapiolani Children's Hospital. He became the Program Director of the Pediatric Residency Program in 1972 and was appointed the Chairman of the Department of Pediatrics at JABSOM in 1973. Dr Hammar is active with the American Academy of Pediatrics, American Board of Pediatrics (ABP) and with the ABP sub-board of Adolescent Medicine.

When asked about the future, Dr Hammar replied "I am totally committed to the success of the School of Medicine. JABSOM, like many, has experienced severe financial crises and has had to cope with many changes. These stresses have forced us to critically review our mission and our goals. Our collaboration and close working relationship with the community hospitals and local health care resources has become exceedingly important and has allowed us to survive. This commitment to the School has been very gratifying and we much continue to develop honest, open, non-competitive collaboration and joint ventures with our community partners. Immediate efforts will be to stabilize the School and to assist the faculty with handling the inevitable changes that are occurring in health care and medical education. Shortly, a search committee for a permanent Dean will be established. In the interim, I am very proud to be part of the transition and optimistic about the future."

Editor's Note:

Chris Gulbrandsen has also been a vital member of the Board of Directors of the Hawaii Medical Library. Many thanks, Chris for your years of support.

I know Sherrel Hammar has the same dedication to our Medical School and our library. Our community is blessed to have men like Chris and Sherrel.

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Medical School Hotline

Implications of Genetic Research for Medical Practice and Education

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How to prepare our physicians and physician trainees for the 21st century? In the 20th century, we witnessed the successes of antibiotics and vaccines and the hope of high technology. The disappearance since World War II of infectious scourges such as smallpox and polio led to the expectation that such remarkable cures and disease eradication would continue. Instead, the diseases that have replaced those epidemics—cancer, heart disease, rheumatologic conditions, diabetes, and psychiatric disorders—have proven much more intractable. There have been undeniable advances in their diagnosis, palliation, and, in the case of some cancers, even cure. By and large, however, the perception is that sophisticated, often expensive procedures have not definitively eradicated or prevented the major scourges of modern society.³

Many of these chronic diseases result from complex interactions between genetic makeup, aging, and the environment, a concept emerging from parallel but reverberating lines of research in epidemiology and molecular and cell biology. These findings raise the hope of a more rational approach to medical care and perhaps even primary prevention of disease. Diet, pollutants, aeroallergens, ultraviolet radiation, infectious agents, and other environmental influences are only part of the puzzle; their effects are critically shaped by genetically determined host responses in susceptible individuals. It will be imperative that the physician of the 21st century understand the genetic determinants of disease as well as he/she understands Koch's postulates for infectious disease or physiological mechanisms of organ dysfunction. This vision will direct innovations and curricular emphases in medical education. The advances in genetic and epidemiological research are occurring so rapidly that it is difficult to select what to present in an already packed curriculum. However, a few signal developments can be highlighted to help physicians and trainees understand the fundamental research and its implications for medical care.

The most common afflictions of modern society appear to be complex traits. That is to say, they have a familial tendency that is not attributable to environmental factors alone, that their inheritance pattern does not follow the classic Mendelian patterns characteristic of single-gene diseases (e.g. recessive, dominant, x-linked), and that the trait or disease is most likely governed by several genes which may be modulated by environmental influences, or which may be inherited differently in different families or ethnic groups. Hypertension, atherosclerosis, type II diabetes, and allergic asthma, for instance, share a polygenic and highly variable nature which can confound efforts to elucidate specific genetic elements.

Because of their polygenic nature, the genetic determinants of complex traits are sought using a different approach. The classic

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- Be active

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method to find genes responsible for single-gene diseases such as thalassemia is to: identify the clinical trait, determine the pattern of inheritance, find the associated biochemical abnormality, isolate the abnormal protein, determine its amino acid sequence, synthesize a DNA probe based on that sequence, and probe the genomic DNA of affected individuals to locate the abnormal gene. How to determine the genetic basis of a complex polygenic disease in which the multiple biochemical and cellular abnormalities have not been entirely elucidated? In a major departure from the approach used for single-gene disorders, the strategy for complex disorders is to identify the clinical trait or phenotype and delve right into the DNA without necessarily isolating specific biochemical abnormalities in the affected persons.^{1,2}

This approach is made possible and productive because many areas of the human genome have now been mapped, some areas in exquisite detail. It is now known not only where genes and gene clusters are, but also the positions of useful genetic markers. These markers are simple sequence repeats (they are called by several similar names)—repeating sequences of 2 to 5 nucleotides which do not encode protein. Over 2,000 simple sequence repeats have already been mapped in the human genome. Their real function is unknown, but they certainly make life easier for genetic cartographers. Indeed, because the position and sequence of each are unique, these repeats serve as longitudes and latitudes on the human genome map.

At least as important, the number of times each sequence repeats varies greatly between individuals. This is a remarkable bonus, because it allows investigators to track how specific genetic elements are inherited. For instance, Dad may have 12 repeats of "D5S436" (a simple sequence repeat on human chromosome 5); Mom may have 6. Depending on how many repeats Junior has, investigators can determine whether he inherited that marker—and any gene close to it—from Mom or from Dad. It can also be determined whether siblings have inherited the same marker from the same parent and are identical by descent at that locus. Using asthma as an example, investigators may surmise that "D5S436" is associated with the phenotypic trait of asthma if 2 siblings with asthma have the same number of repeats of the genetic marker, or if 1 sibling with asthma has 12 repeats and his sibling without asthma has 6 repeats. The strength of this association can be confirmed statistically by studying larger numbers of sibling-pairs. "Sib-pair analysis" is one of the simpler methods of searching for an association between a phenotypic trait and a genetic marker.

There are many permutations of

analysis and the genetic markers to be used (when possible, even putative genes are used as markers), but the general search for phenotypic trait-genetic marker associations—sometimes called "positional cloning"—is a fundamental investigative approach which physicians should understand. It is important to remember that the power of this approach derives from painstaking studies in epidemiology and in the physiologic, cellular, and molecular mechanisms of disease, all of which more specifically define phenotypic traits and putative genes.

The hope is that a better understanding of genetic determinants in susceptible populations will allow coherent understanding of how environmental agents interact with genes to initiate disease. Dietary, hygienic, air quality, or pharmacologic interventions may then be customized for particular groups to achieve more effective and focused management of illness, or even primary prevention of disease. Medicine is already empirical witness to the different efficacy of different classes of anti-hypertensive medications in certain populations. Hopefully, medical education which provides insights into the genetic mechanisms of hypertension and other complex traits will allow physicians to recognize and understand these variations in response to interventions, and to more rationally design management and disease prevention in the 21st century.

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